

MULTIPLE-VARIABLE DOSE REGIMEN FOR TREATING IDIOPATHIC INFLAMMATORY BOWEL DISEASE

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/229,664 (now allowed), filed Mar. 28, 2014, which is a continuation of U.S. patent application Ser. No. 11/104,117, filed Apr. 11, 2005, now U.S. Pat. No. 8,889,136, which claims the benefit of U.S. Provisional Application No. 60/561,139, filed Apr. 9, 2004; U.S. Provisional Application No. 60/561,710, filed Apr. 12, 2004; and U.S. Provisional Application No. 60/569,100, filed May 7, 2004, the contents of each of which applications are hereby incorporated by reference in their entirety.

This application is related to U.S. Pat. Nos. 6,090,382, 6,258,562, and 6,509,015. This application is also related to U.S. patent application Ser. No. 09/801,185, filed Mar. 7, 2001; U.S. patent application Ser. No. 10/302,356, filed Nov. 22, 2002; U.S. patent application Ser. No. 10/163,657, filed Jun. 5, 2002; U.S. patent application Ser. No. 10/133,715, filed Apr. 26, 2002; U.S. patent application Ser. No. 10/222,140, filed Aug. 16, 2002; U.S. patent application Ser. No. 10/693,233, filed Oct. 24, 2003; U.S. patent application Ser. No. 10/622,932, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,039, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,076, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,065, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/622,928, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,075, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,035, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/622,683, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/622,205, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/622,210, filed Jul. 18, 2003; U.S. patent application Ser. No. 10/623,318, filed Jul. 18, 2003; and U.S. patent application Ser. No. 10/422,287, filed Apr. 24, 2003. The entire contents of each of these patents and patent applications are hereby incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically as a text file in ASCII format and is hereby incorporated by reference in its entirety. Said text file, created on Feb. 20, 2015, is named 110222-0010-110_SL.txt and is 12,521 bytes in size.

BACKGROUND OF THE INVENTION

Cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) are molecules produced by a variety of cells, such as monocytes and macrophages, which have been identified as mediators of inflammatory processes. Cytokines, including TNF, regulate the intensity and duration of the inflammatory response which occurs as the result of an injury or infection. Elevated levels of TNF play an important role in pathologic inflammation. TNF also referred to as (TNF α) has been implicated in the pathophysiology of a variety of human diseases and disorders, including sepsis, infections, autoimmune diseases, transplant rejection and graft-versus-host disease (see e.g., Moeller et al. (1990) *Cytokine* 2:162; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A. et al.; Vasilli (1992) *Annu. Rev. Immunol.* 10:411; Tracey and Cerami (1994) *Annu. Rev. Med.* 45:491).

TNF has been implicated in psoriasis. Expression of TNF-induced proteins and the presence of activated T lymphocytes in psoriatic plaques but not uninvolved skin, suggest their involvement in the pathogenesis of the disease. There are several types of psoriasis according to cutaneous manifestations: plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalized pustular and localized pustular psoriasis. Plaque psoriasis is the most common type, however. Treatment of psoriasis depends on the extent of the disease. Topical corticosteroids are commonly used for mild to moderate localized cases. Keratolytic agents and coal tar are also used as topical medications, and phototherapy is commonly used for more widespread disease. Other systemic therapy, such as methotrexate cyclosporine and synthetic retinoids are effective, but are often administered in rotation due to their possible cumulative toxic effect.

TNF has also been implicated in Crohn's disease. Crohn's is diagnosed on the basis of clinical, endoscopic, radiographic, and histologic criteria. The treatment of Crohn's disease is challenging. Treatment is based on location, extent, and severity of disease. Current compounds and regimens do not completely abate the inflammatory process and have significant side effects.

SUMMARY OF THE INVENTION

There is a need to treat TNF α -related disorders, where TNF α activity is detrimental, in a safe and effective manner. The present invention includes multiple-variable dose methods for improved treatment of TNF α -related disorders where TNF α activity is detrimental.

The invention describes a multiple-variable dose method for treating a disorder in which TNF α activity is detrimental, comprising administering to a subject in need thereof at least one induction dose of a TNF α inhibitor such that a threshold level of TNF α inhibitor is achieved within an induction phase; and subsequently administering to the subject at least one treatment dose of the TNF α inhibitor within a treatment phase, such that treatment occurs.

The invention also describes a multiple-variable dose method for treating Crohn's disease, comprising administering to a subject in need thereof at least one induction dose of a TNF α inhibitor such that a threshold level of TNF α inhibitor is achieved within an induction phase; and subsequently administering to the subject at least one treatment dose of the TNF α inhibitor within a treatment phase, such that treatment occurs. The multiple-variable dose method of the invention can also be used to treat ulcerative colitis or psoriasis. In another embodiment, multiple-variable dose method of the invention is used to treat as psoriasis in combination with psoriatic arthritis.

The invention includes a multiple-variable dose method of inducing remission of Crohn's disease, comprising administering to a subject in need thereof at least one induction dose of a TNF α inhibitor such that a threshold level of TNF α inhibitor is achieved within an induction phase; and subsequently administering to the subject at least one treatment dose of the TNF α inhibitor within a treatment phase, such that treatment occurs.

In an additional embodiment, the invention includes a multiple-variable dose method of reducing psoriatic plaques comprising administering to a subject in need thereof at least one induction dose of a TNF α inhibitor such that a threshold level of TNF α inhibitor is achieved within an induction phase; and subsequently administering to the subject at least one treatment dose of the TNF α inhibitor within a treatment phase, such that treatment occurs.